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Synthesis of benzyl-beta-d alcohol for use in studies of photolytic solvolysis reactions

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SYNTHESIS OF BENZYL-\textalpha-\textdelta ALCOHOL
FOR USE IN STUDIES OF PHOTOLYTIC
SOLVOLYSIS REACTIONS

by

John Crest Anes  \textcopyright UC 1969

Senior Thesis Submitted
in Partial Fulfillment
of the Requirements of Graduation

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This Thesis

Submitted by

John C. Ames

to the
Department of Chemistry of Union College
in partial fulfillment of the requirements of the degree of Bachelor of Science with a Major in Chemistry

is approved by

Alan L. Meacock
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ABSTRACT

This project proposes a means for determining whether certain photochemical solvolysis reactions proceed by an $S_N^1$ or $S_N^2$ type mechanism. The method uses optically active substrates to determine whether the displacement reaction occurs with racemization or retention of configuration.

This paper deals with the synthesis of optically active benzyl-$\alpha$-$d$ alcohol from which various appropriate substrates required for the study can be prepared. Benzaldehyde-$d$ is first prepared by the Stephens reduction of benzonitrile using stannous chloride and deuterium chloride. The optically active alcohol is then prepared by the reduction of the benzaldehyde-$d$ with optically active isobornylmagnesium bromide.
Zimmerman (1) has shown that several benzyl compounds when irradiated undergo both free radical and ionic (solvolytic) reactions. As shown in Figure 1, if 4-methoxybenzyl acetate is photolyzed in aqueous dioxane mainly free radical products are obtained. If 3-methoxybenzyl acetate is treated similarly, greater quantities of 3-methoxybenzyl alcohol than of free radical products are formed. No dark reactions are observed under identical conditions.

Figure 1. Zimmerman's photolytic solvolytic reactions

The photochemical excitation for this type of reaction is of the $\pi-\pi^*$ type. Using molecular orbital calculations it is found that in contrast to the ground states, which show ortho-para electron withdrawal for an electron withdrawing group on a benzene ring, and ortho-para donation by electron donating groups, the excited states show selective ortho electron withdrawal from the ortho and meta positions by
withdrawing groups and a similar **ortho-meta** donation by donating groups (1).

This is shown in Figure 2.

![Figure 2. Monosubstituted benzene electron densities with W= CH₂⁺, D = CH₂⁻. (1)](image)

Zimmerman’s observations are in direct accord with these molecular orbital calculations which show that ionic (solvolytic) reactions (vs. the radical ones) should be more favorable with **meta** donating groups than with **para** donating ones.

The following mechanism was formulated by Zimmerman for the solvolytic reaction. The purpose of this project is to determine whether this reaction proceeds through a free carbonium ion intermediate (Sₐ₁) or proceeds by means of a concerted process with the acetate ion leaving as the nucleophile (hydroxyl ion in this case) attacks (Sₐ₂). This can be achieved by photolyzing the appropriate optically active substrates.
Reaction 4 was chosen for study because Zimmerman has run this type of reaction successfully and various optically active derivatives of benzyl-\(\alpha\)-d alcohol for use as substrates are known (2). It was felt that even if the benzene ring lacks the meta donating substituent, enough of the ether product should be formed to allow a stereochemical study.

**DISCUSSION**

If the solvolysis of optically active deuterated benzyl acetate proceeds through a carbonium ion intermediate (\(S_N1\)) the benzyl-\(\alpha\)-d ethyl ether formed will not be optically active as the ethanol could attack the deuterated carbon from either side of the planar carbonium ion. If, however, the reaction is a concerted process (\(S_N2\)) then inversion about the deuterated carbon would occur and an optically active ether product would result.
First the optical rotation of the benzyl-\(\alpha\)-d ethyl ether, formed from the same benzyl-\(\alpha\)-d alcohol from which the benzyl-\(\alpha\)-d acetate was prepared would have to be determined. Following the scheme shown in Figure 5 with all the products optically active, the acetate and the ether would have the opposite configuration about the deuterated carbon.

Reaction 4 would be run and following the isolation of the ether product from the reaction mixture, its optical rotation would be determined. If the reaction is \(S_N1\), then the product will be racemic. If it is \(S_N2\), the product will be optically active and its specific rotation should be the same as that ether obtained in Figure 5 since inversion has occurred about the deuterated carbon. A partially racemic mixture would indicate that both \(S_N1\) and \(S_N2\) pathways were followed and the percentage of each would be determined.

The synthesis of benzyl-\(\alpha\)-d alcohol used is a modification of the procedure used by Streitwieser (2) and is outlined below.
For the first run no benzoyl chloride was available, so it was prepared by adding thionyl chloride to benzoic acid (3). The following reactions occur:

\[
C_6H_5-COOH + SOCl_2 \rightarrow C_6H_5-COCl + SO_2 + HCl
\]

Deuterium chloride was prepared by adding deuterium oxide to benzoyl chloride (4).

\[
\begin{align*}
C_6H_5-\text{Cl} + D_2O & \rightarrow C_6H_5-\text{OD} + DCl \\
C_6H_5-\text{C-OD} + C_6H_5-\text{C-Cl} & \rightarrow (C_6H_5CO)_2O + DCl
\end{align*}
\]

In this manner two moles of deuterium chloride are produced for each mole of deuterium oxide used.

The deuterium chloride was then passed into a suspension of the stannous chloride, which had been dehydrated with acetic anhydride (5), after which benzonitrile was added. The reaction mixture was hydrolyzed to yield benzaldehyde-d according to the stoichiometry from the equation below. The benzaldehyde was purified by means of a sodium bisulfite addition compound.

\[
C_6H_5-CN + 3 DCl + SnCl_2 \rightarrow C_6H_5CDND\cdot DCl + SnCl_4
\]

\[
C_6H_5CDND\cdot DCl + H_2O \rightarrow C_6H_5CDOD
\]

Since Slotta and Kethur (6) have found that stannous chloride will not dissolve in ether when hydrogen chloride is passed through it unless a small amount of water is present (our stannous chloride did dissolve), the benzaldehyde-d obtained by this method should not be isotopically pure. This is borne out by the fact that the infrared spectrum of the benzaldehyde-d obtained did have a slight triplet centered at 3.6 \(\mu\) characteristic of C-H stretching.

Optically active isoborneol was obtained by the reaction of \(d\)-camphor and lithium aluminum hydride according to the method of Noyce (7).
Steric hinderance by the methyl groups forces the lithium aluminum hydride to attack only from the underside of the ring thus yielding only isoborneol.

Optically active isobornylmagnesium bromide is prepared to achieve a stereospecific reduction of benzaldehyde-$d$ by means of a Meerwein-Pondorf-Oppenhauer-Verley reaction (3). $n$-Propylmagnesium bromide, prepared from $n$-propyl bromide and magnesium, reacts with the isoborneol to give the desired isobornylmagnesium bromide, which is used to stereospecifically reduce the benzaldehyde-$d$ to yield benzyl-$d$ alcohol. Due to steric hinderance and preferred
orientation of the molecules for formation of new bonds, the benzyl-\( \alpha \)-d alcohol thus formed is optically active.

The crude benzyl-\( \alpha \)-d alcohol is purified by adding phthalic anhydride to yield hydrogen benzyl-\( \alpha \)-d phthalate.

\[
\begin{align*}
\text{CHDOH} & \quad + \quad \begin{array}{c}
\text{C} \\
\text{O}
\end{array} & \quad \rightarrow & \quad \begin{array}{c}
\text{C} \\
\text{O} \\
\text{D} \\
\text{C}_6\text{H}_5
\end{array}
\end{align*}
\]

Cleavage by lithium aluminum hydride is then used to generate the purified benzyl-\( \alpha \)-d alcohol.

For this compound Streitwieser (2) reports \( \alpha \)\(_D\)^{25} = 1.3° (12).

For this project, we first ran through the reactions twice using undeuterated reactants to become familiar with the various reactants and equipment. Then we ran the actual synthesis of the optically active alcohol. This synthesis was carried up through the formation of crude benzaldehyde-d. The experimental section is, therefore, not given in a chronological order but rather in the proper order for the synthesis.
EXPERIMENTAL

Benzoyl Chloride Formation (3)

Benzoic acid (530 g, 4.4 mol) was added to 1,000 g (8.4 mol) of thionyl chloride. The mixture was allowed to reflux for 1 hr. Reduced-pressure distillation of the mixture yielded 500 g of yellowish benzoyl chloride. This process was then repeated to give a combined yield of 980 g (79%) of crude benzoyl chloride.

Anhydrous Stannous Chloride Formation (5)

Stannous chloride hydrate (246 g, 1.00 mol) was added with stirring to 204 g (2.00 mol) of acetic anhydride. The mixture was stirred for 1 hr then filtered, and the anhydrous stannous chloride was washed with two 60 ml portions of anhydrous ether. The stannous chloride was then dried for 48 hr in a vacuum dessicator over calcium chloride. A total of 200 g (95%) of anhydrous stannous chloride was obtained. For a second run the yield was 89%.

Deuterium Chloride Formation (4)

The deuterium chloride was generated over a period of 8 hr by slowly dropping 20 g (1.0 mol) of deuterium oxide through a condenser into 1,000 g (7.5 mol) of stirred, freshly distilled benzoyl chloride in a 3 l flask. When all the deuterium oxide had been added, the mixture was gently heated until gas was no longer evolved. The deuterium chloride was delivered to the reaction vessel as described below.

Benzaldehyde-d Formation (2)

Into a 2 l three-necked flask fitted with a gas dispersion tube, mechanical stirrer, condenser, dropping funnel, and with a nitrogen
atmosphere was distilled 1 l of ether from calcium hydride. To this was added 200g (0.95 mol) of anhydrous stannous chloride. A total of 2.0 mol of deuterium chloride (see above) was then passed through a dispersion tube into the stirred suspension. Most of the stannous chloride dissolved in the ether to form a clear solution. Then 42g (0.41 mol) of benzonitrile was added rapidly from the dropping funnel and the solution was vigorously stirred for 1 hr and then allowed to stand for 48 hr. After this time there were two phases, a yellowish ethereal phase and a white crystalline solid. The ether was removed by decantation and the residue washed twice with anhydrous ether. Water(800 ml) was then added to the residue and the solution was made basic to bromophenol blue by the addition of solid sodium bicarbonate. The mixture was brought to boiling and steam distilled until about 400 ml of distillate was obtained. There has as yet been no confirmation of the 12 g of crude product thus obtained. An infrared spectrum (neat) of about 1 ml of crude product obtained in a trial run showed the C-D bands of benzaldehyde-d at 4.73, 4.83, and 4.87 μ, the C-H bands of benzaldehyde at 3.50, 3.54, and 3.65 μ and a band at 4.5 μ showing there was still some unreacted benzonitrile in the mixture.

From here on, the experimental procedures are those worked out using nondeuterated compounds.

Isoborneol Formation (7)

Over a period of 1 hr 10g (0.066 mol) of camphor in 35 ml of anhydrous ether was added to a stirred refluxing suspension of 3.0g (0.08 mol) of lithium aluminum hydride in 150 ml of anhydrous ether.
The mixture was refluxed for 12 hr to ensure complete reaction. The excess lithium aluminum hydride was then destroyed with ethyl acetate. About 100 ml of 3N HCl was added to hydrolyze the mixture. The ether layer was separated, washed with sodium bicarbonate and dried over anhydrous sodium sulfate. The ether was evaporated leaving a dull white solid which was sublimed twice to yield 715g (75%) of white isoborneol. An infrared spectrum (neat) of this product showed a strong hydroxyl peak at $3.4 \mu$ and a very slight carbonyl peak at $5.9 \mu$. This confirms the almost complete formation of isoborneol from camphor. In an earlier run the camphor and lithium aluminum hydride were refluxed for only 4 hr and the infrared spectrum showed there was still an appreciable amount of camphor left as evidenced by a rather strong carbonyl peak at $5.9 \mu$.

**Benzyl Alcohol Formation (2)**

n-Propyl bromide (5.8 ml, approx. 0.06 mol, 90% pure) in 40 ml of anhydrous ether was added to 1.4g (0.050 g-atom) of magnesium turnings in 60 ml of anhydrous ether. The reaction proceeded immediately and after 1 hr of heating all the magnesium turnings had reacted. Then 7.5g (0.06 mol) of isoborneol in 30 ml of anhydrous ether was added using an equalizing pressure dropping funnel. This mixture was then refluxed overnight with stirring. The isobornyloxymagnesium bromide was in the form of a white precipitate. The ether was removed by distillation thru a Hempel column filled with glass beads. The new solvent, 80 ml of dry benzene, was added to the residue and the mixture was heated to 72° to drive off the last traces of ether.

Benzaldehyde (3.0g, 0.027 mol) was added to the cooled mixture which was stirred overnight. Two phases, a yellowish liquid phase
and a white solid phase, were present after 100 ml of water was added. After decantation of the organic phase, the aqueous phase was extracted several times with ether. The combined organic layers were then dried with anhydrous potassium carbonate and the solvents were removed by distillation. About 70 ml of water was then added and the distillation continued until a white layer began to form on the condenser. At this point the condenser was placed directly on the flask and the aqueous mixture was refluxed. The camphor and isoborneol then solidified in the condenser. Two condensers were used, one being cleaned while the other was in use. This was continued until all the camphor and isoborneol were removed. Then 60g of potassium carbonate was added to reduce the solubility of the benzyl alcohol and the mixture was extracted with ether. The organic mixture was dried with anhydrous potassium carbonate and the ether was evaporated. About 1.6g (51%) of crude benzyl alcohol was obtained. An infrared spectrum of the residue on the condensers showed that it was mostly camphor, thus indicating the reaction had run successfully. An NMR spectrum of the product showed it to be benzyl alcohol.

**Purification of the Benzyl Alcohol (2)**

To 10.4g (0.10 mol) of benzyl alcohol was added 14.8g (0.10 mol) of phthalic anhydride. The mixture was stirred at 110° for 22 hr, poured into 500 ml of water containing 17.3g (0.125 mol) of potassium carbonate, stirred for 1 hr and then washed with ether to remove the undissolved solid. An oily layer formed after acidification to pH 2 with conc. hydrochloric acid. When cooled to 0° the oily layer solidified to a white crystalline solid which was filtered off. After recrystallization from a benzene-cyclohexane mixture (100 ml of each) 22.5 g (95%) of hydrogen benzyl phthalate was obtained. To 12g (0.045 mol)
of hydrogen benzyl phthalate in 100 ml of tetrahydrofuran was added 4.75g (0.125 mol) of lithium aluminum hydride. The mixture was stirred and heated at 60-70° over a weekend. The excess lithium aluminum hydride was destroyed with 22 ml of ethyl acetate and the mixture hydrolyzed with 3N hydrochloric acid. The tetrahydrofuran layer was separated, washed with sodium bicarbonate, and dried over sodium sulfate. Distillation then yielded 3.9g (79%) of benzyl alcohol, nD 1.5096 (lit. (8) nD 1.5071).

**Benzyl Acetate Formation (2)**

Acetyl chloride (3.9g, 0.05 mol) was added to an ice cold stirred solution of 4.0g (0.037 mol) of benzyl alcohol, 15 ml of pentane and 8 g of pyridine. The mixture was stirred overnight at room temperature after which it was diluted with pentane, washed with dilute acid and dried over anhydrous sodium sulfate. Distillation through a Hempel column filled with glass beads at 12 mm pressure gave 5.0g of a yellowish liquid. Redistillation yielded 4.6g (84%) of benzyl acetate bp 101° (12mm) (lit. (2) bp 99° (10mm)).
BIBLIOGRAPHY


